REMARKS

Applicant respectfully requests reconsideration.

Claims 1-53 were pending in this application. Claims 4-7, 15-20, 25, 26, 30-33 and 41-52 have been withdrawn as being drawn to nonelected inventions. Claims 2, 3, 8-10, 12, 14, 22-24, 29, 34-36, 38 and 40 have been canceled without prejudice or disclaimer. Claims 1, 11, 13, 21, 27, 28, 37, 39, 47 and 53 have been amended. Support for the amendments can be found throughout the specification and in the claims as originally filed. Applicant reserves the right to pursue the subject matter of the originally filed claims in one or more continuing applications. Claims 1, 11, 13, 21, 27, 28, 37, 39, 47 and 53 are currently under examination.

No new matter has been added.

Objections to the Specification

The Examiner has stated that the substitute specification filed 10/21/05 has not been entered because it allegedly does not conform to 37 CFR 1.125(b) inasmuch as it is not accompanied by a statement that the substitute specification includes no new matter.

Applicant's attorney states for the record that the previously filed substitute specification includes no new matter. A separate statement according to 37 CFR 1.125(b) that the substitute specification filed 10/21/05 includes no new matter accompanies this amendment.

Claim Objections

The Examiner has stated that should claim 36 be found allowable, claim 38 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. The Examiner has further objected to Claim 38 under 37 CFR 1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has canceled claims 36 and 38 without prejudice or disclaimer. Reconsideration and withdrawal of the objection is respectfully requested.

The Examiner has objected to claim 8 because the limitation "the agent that inhibits Stat5 activity" allegedly lacks literal antecedent basis. Applicant has canceled claim 8 without prejudice or disclaimer. Reconsideration and withdrawal of the objection is respectfully requested.

The Examiner has objected to claim 3 because of a missing "of" between "the inhibitor" and "Stat5" in line 1 of the claim. Applicant has canceled claim 3 without prejudice or disclaimer. Reconsideration and withdrawal of the objection is respectfully requested.

The Examiner has objected to claims 3, 10, 12, 14, 23, 24, 28, 29, 36, 38 and 40 for reciting non-elected subject matter. Applicant has canceled claims 3, 10, 12, 14, 23, 24, 29, 36, 38 and 40 without prejudice or disclaimer. Applicant has amended claim 28 to cancel the non-elected subject matter. Reconsideration and withdrawal of the objection is respectfully requested.

Rejections under 35 U.S.C §112

The Examiner has rejected claims 1, 2, 21, 22, 23, 27, 28, 47, and 53 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

Applicant respectfully traverses. Applicant submits that the previously pending claims met the written description requirement. The previously pending claims were drawn to methods of inhibiting prostate cancer cell growth, comprising inhibiting Stat5 activity in prostate cancer cells; methods of treating prostate cancer in males, comprising administering to males therapeutically effective amounts of agents that inhibit the activity of Stat5 in prostate cancer cells; and pharmaceutical compositions comprising inhibitors of Stat5 activity. The family of Stats, including Stat5a and Stat5b, and their involvement in prostate cancer is taught in the instant specification, e.g. on page 11, line 9 to page 15, line 2. Further, the specification teaches numerous inhibitors of Stat5 activity, including inhibitors of phosphorylation, inhibitors of DNA binding, antisense molecules, siRNA molecules, dominant-negative competitors, ribozymes, and antibodies (see, e.g. page 17, line 14 to page 24, line 27). In addition, the specification teaches administration regimens and pharmaceutical compositions, for example on page 25, line 1 to page 27, line 9. In view thereof, Applicant had possession of the subject matter of the rejected claims, as previously pending, at the time of filing.

Nevertheless, without conceding the correctness of the Examiner's argument and solely in the interest of expediting prosecution, Applicant has amended independent claims 1, 27 and 53 to recite methods of inhibiting prostate cancer cell growth, comprising inhibiting Stat5b polypeptide activity in prostate cancer cells by contacting the cells with siRNA inhibitors of Stat5b activity

(claim 1); methods of treating prostate cancer in a male, comprising administering therapeutically effective amounts of siRNAs that inhibit the activity of Stat5b polypeptides in prostate cancer cells of the male (claim 27); and pharmaceutical compositions comprising siRNA inhibitors of Stat5b activity (claim 53), respectively.

The relevant inquiry in analyzing written description is whether the specification "clearly allows persons of ordinary skill in the art to recognize that the applicant has in fact invented what is claimed" (In re Gosteli, 872 F.2d 1008, 1012 (Fed. Cir. 1989)) or, in other words, that the applicant was in "possession" of the invention (In re Alton, 76 F.3d 1168, 1175 (Fed. Cir. 1996)).

The claims as now amended are directed to methods of inhibiting prostate cancer cell growth, comprising inhibiting Stat5b polypeptide activity in prostate cancer cells by contacting the cells with siRNA inhibitors of Stat5b activity; methods of treating prostate cancer in a male, comprising administering therapeutically effective amounts of siRNAs that inhibit the activity of Stat5b polypeptides in prostate cancer cells of the male; and pharmaceutical compositions comprising siRNA inhibitors of Stat5b activity.

The specification teaches Stats, including Stat5b, and its involvement in prostate cancer (e.g. on page 11, line 9 to page 15, line 2). The specification teaches siRNA molecules (e.g. on page 19, line 18 to page 21, line 7), as well as pharmaceutical compositions comprising siRNA and their administration (e.g. on page 25, line 1 to page 27, line 9).

The Examiner acknowledges that the specification adequately describes siRNA constructs targeted to Stat5b "by fully setting forth their structures and functions, and by describing the materials and methods needed to make and use such agents" (page 7 of the Office Action). The Examiner further acknowledges that "methods comprising the use of siRNA [...] meet the written description requirement" (page 8 of the Office Action).

From the teachings provided in the specification, one of ordinary skill in the art would recognize that Applicant clearly had, at the time of filing, possession of methods of inhibiting prostate cancer cell growth, comprising inhibiting Stat5b polypeptide activity in prostate cancer cells by contacting the cells with siRNA inhibitors of Stat5b activity; methods of treating prostate cancer in a male, comprising administering therapeutically effective amounts of siRNAs that inhibit

the activity of Stat5b polypeptides in prostate cancer cells of the male; and pharmaceutical compositions comprising siRNA inhibitors of Stat5b activity.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C §102

The Examiner has rejected claims 1, 2, 21, 22, 27, and 53 under 35 U.S.C. §102(e) as being anticipated by Shaw et al. (WO 03/026641), as evidenced by Leong et al. (2002) *Oncogene* 21:2846-2853. The Examiner argues that Shaw et al. disclose and claim a method for using a Stat5b inhibitor to treat prostate carcinoma and that methods for making and using Stat5b inhibitors were known in the art, as evidenced by Leong et al.

Applicant respectfully disagrees. Shaw et al. as evidenced by Leong et al. do not anticipate the claims as now amended.

The standard for anticipation has been stated as follows: "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Although Shaw et al. refer to Stat 5 inhibitors, its focus is the effects of specific chemical compounds, e.g. N-(3-oxo-dodecanoyl)-L-homoserine lactone (OdDHL), on Stat1 and Stat3 activation, complex formation and DNA binding in the context of cell proliferation and apoptosis in various breast cancer cell lines. They do not discuss or mention SiRNA inhibitors. Leong et al. teach the use of antisense oligonucleotides or dominant-negative mutant Stat5b in inhibiting growth of squamous cell carcinoma cells of the head and neck (SCCHN).

Shaw et al. and Leong et al. do not teach a method of inhibiting prostate cancer cell growth, comprising contacting prostate cancer cells with an siRNA inhibitor of Stat5b activity. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C §103

The Examiner has rejected claims 3, 8-14, 23, 24, 28, 29, 34-40, and 47 under 35 U.S.C. §103(a) as being unpatentable over Shaw et al. (WO 03/026641) and further in view of Leong et al.

(2002) *Oncogene* 21:2846-2853; Turkson et al. (2000) *Oncogene* 19:6613-6626; Ahonen et al. (2002) *Endocrinology* 143:228-238; and Tuschl et al. (US2004/0259247).

Applicant respectfully disagrees. A finding of obviousness is based on the factual analysis set forth in Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966), which was affirmed by the US Supreme Court in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385 (2007). See also MPEP 2141. The factual inquiry of Graham v. John Deere includes: 1) determining the scope and content of the prior art; 2) ascertaining the difference between the claimed invention and the prior art, considering both the prior art and the invention as a whole; and 3) resolving the level of ordinary skill in the art. Notwithstanding these factual inquiries, objective evidence of obviousness or non-obviousness must also be considered before reaching a conclusion on obviousness. Objective evidence includes: (1) the commercial success of the invention; (2) whether the invention satisfied a long felt need in the industry; (3) failure of others to find a solution to the problem at hand; and (4) unexpected results.

Applicant respectfully submits that the combined teachings of Shaw et al. (WO 03/026641), Leong et al. (2002), Turkson et al. (2000), Ahonen et al. (2002), and Tuschl et al. (US2004/0259247) do not render the claimed invention obvious.

Shaw et al. list at least 37 broad compound classes encompassing hundreds of molecules, one class of which is Stat5b inhibitors, for the treatment of at least 23 different kinds of cancers, one of which is prostate cancer, as well as for the treatment of at least five additional non-cancer diseases (see, page 3, lines 4-22). No concrete teaching is provided linking any of the large compound classes to any of the many diseases listed, except for Stat1 and Stat3 inhibitors in the context of breast cancer.

In a recently decided Federal Circuit case the court stated that "KSR posits a situation with a finite, and in context of the art, small or easily traversed number of options that would convince an ordinarily skilled artisan of obviousness" [Emphasis added]. (Ortho-McNeil v. Mylan Laboratories, slip op. at 9 (Fed. Cir. 2008)).

Shaw et al. do not provide any specific suggestion that prostate cancer could be treated using Stat5b inhibitors. There is only one concrete teaching concerning Stat5a and 5b is that "the absence

of Stat 5a and 5b causes defects in T cell growth" (see, page 2, 2nd paragraph). This teaching does not allow a person of ordinary skill in the art to draw any conclusions as to the role of Stat5 in prostate cancer, or the usefulness and desirability of Stat5 inhibitors for inhibiting prostate cancer cell growth. Shaw et al. only provide a very large number of possible combinations of hundreds of molecules and dozens of diseases, and specifically teach the effects of certain chemical compounds, e.g. N-(3-oxo-dodecanoyl)-L-homoserine lactone (OdDHL), on Stat1 and Stat3 in the context of cell proliferation and apoptosis in various breast cancer cell lines. Shaw et al. provide no teaching that would make it possible or even motivate one of ordinary skill in the art to go beyond what is taught with regard to Stat1 and Stat3 and to choose the particular combination of "Stat5b inhibitor" and "prostate cancer" from the very large number of possible combinations.

Further, there can be no reasonable expectation of success. Without *a priori* knowledge of the biological function of Stat5 a person of ordinary skill in the art would not know what effect activated Stat has, for any given cancer type, for example if Stat5 promotes or inhibits cell proliferation, apoptosis, or differentiation or has any other influence on the cell cycle.

In fact, it has been shown by Applicant that Stat5 is a critical survival factor for prostate cancer cells and its activation predicts poor clinical outcome of prostate cancer. However, in contrast to prostate cancer, the role of Stat5a/b in breast cancer appears to be opposite since activation of Stat5a/b predicts favorable clinical outcome (see, e.g. Nevalainen et al., J Clin Oncology, 2004).

Therefore, if a person of ordinary skill in the art, following the teachings of Shaw et al, would give Stat5 inhibitor to breast cancer patients, the inhibitor may have detrimental effects on the patients and their clinical outcome. This clearly shows that the teachings of Shaw et al contain potentially many inoperative combinations.

Leong et al., Turkson et al., Ahonen et al., and Tuschl et al. do not supply what Shaw et al. lack.

Leong et al. teach the use of antisense oligonucleotides to target Stat5b in squamous cell carcinoma, and teaches that Stat5 is activated primarily in leukemia, such as ALL, CLL, CML, and AML. Leong et al. do not even suggest that Stat5b activation is associated with prostate cancer.

Further, Leong et al. teach that Stat5b expression is important for proliferation of SCCHN cells and that antisense oligonucleotides that inhibit Stat5b expression cause inhibition of cell proliferation. Prostate cancer cells, however, proliferate very slowly, and thus a person of ordinary skill in the art would not consider prostate cancer cells to be good targets for (therapeutic) agents that inhibit cell proliferation, representing a teaching away from the instantly claimed methods and compounds. The instant specification, on the other hand, provides the rationale to treat prostate cancer cells with Stat5b inhibitors, because, as taught therein, Stat5b is required for survival of prostate cancer cells.

The teachings of Turkson et al. focus predominantly on Stat3 in cancer development and as a drug target. Applicant submits that the Examiner has taken the quote from the abstract of Turkson et al. that " particularly Stat3 and Stat5 [are] associated with a wide variety of human malignancies, including hematologic, breast, head and neck, and prostate cancer" out of context. Turkson et al. do not teach that *both* Stat3 and Stat5 are associated with the malignancies listed. Instead, it becomes clear from the teachings of the reference as a whole which Stat is associated with a given malignancy. The authors list Stat3 as being the *sole* Stat family member activated in prostate cancer, see Table 1 on page 6616. Stat3 together with Stat1is also associated with breast and head and neck cancers. The authors list Stat5 activation for certain brain tumors, lymphomas, and leukemias (i.e. hematologic cancers), such as ALL, CML, and AML, but not for prostate cancer. Thus, the teachings of Turkson et al. clearly represent a teaching away from the instantly claimed methods and compounds.

Ahonen et al. discuss the phosphorylation, activation and translocation to the nucleus of Stat5a and 5b in normal rat prostate organ culture upon PRL (prolactin) stimulation. They teach that PRL stimulates proliferation, suppresses apoptosis and causes epithelial hyperplasia in prostate tissue cultures. Ahonen et al. propose that Stat5a and 5b phosphorylation-mediated signaling is "*one candidate* signaling mechanism, used by PRL and possibly other growth factors and cytokines, that supports the viability of prostate epithelial cells during long-term androgen deprivation" (see, Abstract, page 228, emphasis added). The Examiner alleges that Ahonen et al. teach that "therapy-based killing of prostate cancer cells *may* require combined blockade of distinct signaling pathways

of several growth factors and cytokines, among which Stat5 proteins *may* provide good candidate target" (see, page 237, emphasis added). More accurately, Ahonen et al. merely speculate that Stat5b proteins may be a good candidate target. Ahonen et al. do not teach the expression or activation of Stat5 in human prostate cancer cells or tissue or that active Stat5 is important for the development and/or maintenance of prostate cancer cells. Ahonen et al. state that the combined blockade of distinct signaling pathways of several growth factors and cytokines (such as e.g. MAPK) may be required for the killing of prostate cancer cells. This is NOT a teaching that specifically inhibiting Stat5 function would induce cell killing in human prostate cancer cells, and Ahonen et al. provide no description of how this might be done.

Therefore, the prior art cited by the Examiner, when considered as a whole does not teach that Stat5 was activated in human prostate cancer and further teaches that other Stats were activated instead (see e.g. Shaw et al., Leong et al. and Turkson et al.). In addition, the specification cites a report by Ni et al. J Urol. 2002 Apr;167(4):1859-62, (copy enclosed and cited in IDS) describe that only Stat3 and Stat6 are selectively activated in prostate cancer.

Although Tuschl et al. describe siRNA in general, they do not teach or suggest siRNA specific for Stat5 or provide any teachings related to prostate cancer cell growth.

At the time the application was filed, the role of Stat5 in human prostate cancer development and progression had not been established in the prior art and the concept of transcription factor Stat5 as a survival factor in prostate cancer was unknown until Applicant's work established this concept. The results obtained by Applicant for inhibiting prostate cancer cell growth and inducing cell killing based on inhibiting or blocking the activity of Stat5 were unexpected, particularly in view of the published literature and prevailing views within the scientific field.

A person of ordinary skill in the art would not have been motivated to target Stat5 to inhibit prostate cancer cell growth. In fact, the prior art as a whole suggested activation of Stats other than Stat5, such as e.g. Stat3, in prostate cancer. A person of ordinary skill in the art would not have had an expectation of success that inhibiting Stat5 would kill prostate cancer cells based on the teachings of the prior art considered as a whole, and particularly Leong et al. (suggesting Stat5 inhibition for rapidly proliferating cancer cells, as opposed to slow growing prostate cancer cells),

Turkson et al. and Ni et al. (both suggesting the involvement of Stats other than Stat5 in prostate cancer). Further, a person of ordinary skill in the art would not have selected the specific combination of Stat5 inhibitors and prostate cancer out of the very large number of possible combinations of agents and diseases disclosed in Shaw et al. without additional suggestion that this combination would be desirable, which the art cited by the Examiner does not supply.

The instant claims relating to methods of inhibiting prostate cancer cell growth, comprising inhibiting Stat5b polypeptide activity in prostate cancer cells by contacting the cells with siRNA inhibitors of Stat5b activity and methods of treating prostate cancer in a male, comprising administering therapeutically effective amounts of siRNAs that inhibit the activity of Stat5b polypeptides in prostate cancer cells of the male are not obvious in view of the prior art. The Examiner has failed to make a *prima facie* case of obviousness.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Art made of record but not currently relied on

The Examiner states that the following post-filing art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure: Xi et al. (2003) Cancer Res. 63:6763-6771 and Kazansky et al. (2003) Cancer Res. 63:8757-8762.

For the record, Applicant notes that the art cited by the Examiner is post-filing art. Applicant does not concede the correctness of the Examiner's characterization of the references and reserves the right to fully respond to the Examiner's characterization of these references should these references be cited in a rejection.

CONCLUSION

Applicant believes that no further fee in addition to the appropriate Extension of Time fee is due with this Reply. However, if a fee is due, the Director is hereby authorized to charge the required fees to the American Express account associated with Wolf, Greenfield & Sacks, P.C. The Director is authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 23/2825, under Docket No. G0762.70004US01.

In view of the above amendments and discussion, Applicants believe the pending application is now in condition for allowance. Allowance is respectfully requested.

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Respectfully submitted,

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